Sample Size and Power

Chapter 22, 3rd Edition
Chapter 15, 2nd Edition

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Disclaimer

• This presentation reflects the views of the author and should not be construed to represent FDA’s views or policies.

Why care about sample size and power?

Power = probability of getting a statistically significant result, when in fact there is a ‘clinically’ meaningful difference (unknown to us)

By definition, studies with low power are less likely to produce statistically significant results, even when a clinically meaningful effect does exist

Lack of statistical significance does not prove that there is no treatment effect, but instead may be a consequence of small sample size (i.e. low power)

Therefore, it is important to have enough power and an adequate sample size
Objectives

- Calculate changes in sample size based on changes in the difference of interest, variance, or number of study arms
- Understand intuition behind power calculations
- Recognize sample size formulas for the tests
- Learn tips for getting through an IRB

Take Away Message

- Get some input from a statistician
  - This part of the design is vital and mistakes can be costly!
- Take all calculations with a few grains of salt
  - “Fudge factor” is important!
- Round UP, never down (ceiling)
  - Up means 10.01 becomes 11
- Analysis Follows Design

Take Home: What you need for N

- What difference is scientifically important in units – *thought, discussion*
  - 0.01 inches?
  - 10 mm Hg in systolic blood pressure?
- How variable are the measurements (accuracy)? – *Pilot!*
  - Plastic ruler, Micrometer, Caliper
Sample Size

- Difference (effect) to be detected ($\delta$)
- Variation in the outcome ($\sigma^2$)
- Significance level ($\alpha$)
  - One-tailed vs. two-tailed tests
- Power
- Equal/unequal arms
- Superiority or equivalence or non-inferiority

Vocabulary

- Follow-up period
  - How long a participant is followed
- Censored
  - Participant is no longer followed
    - Incomplete follow-up (common)
    - Administratively censored (end of study)
- More in my next lecture

Question

Without _______?_____, there is no need for Statistics.
Answer

Without *variability*, there is no need for Statistics

Variability

Old Treatment | New Treatment
---|---
Average | Average

Variability

Old Treatment | New Treatment
---|---
Average | Average
Variability

<table>
<thead>
<tr>
<th>Old Treatment</th>
<th>New Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td>Average</td>
</tr>
</tbody>
</table>

Outline

- Power
  - Basic Sample Size Information
  - Examples (see text for more)
  - Changes to the basic formula
  - Multiple comparisons
  - Poor proposal sample size statements
  - Conclusion and Resources
Power Depends on Sample Size

- Power = 1-\(\beta\) = P( reject H_0 \mid H_1 \text{ true} )
  - “Probability of rejecting the null hypothesis if the alternative hypothesis is true.”
- More subjects \(\Rightarrow\) higher power

Power is Affected by…..

- Variation in the outcome (\(\sigma^2\))
  - \(\downarrow\) \(\sigma^2\) \(\rightarrow\) power \(\uparrow\)
- Significance level (\(\alpha\))
  - \(\uparrow\) \(\alpha\) \(\rightarrow\) power \(\uparrow\)
- Difference (effect) to be detected (\(\delta\))
  - \(\uparrow\) \(\delta\) \(\rightarrow\) power \(\uparrow\)
- One-tailed vs. two-tailed tests
  - Power is greater in one-tailed tests than in comparable two-tailed tests

Power Changes

- 2n = 32, 2 sample test, 81% power, \(\delta=2\), \(\sigma = 2\), \(\alpha = 0.05\), 2-sided test
- Variance/Standard deviation
  - \(\sigma: 2 \rightarrow 1\) Power: 81\% \(\rightarrow\) 99.99\%
  - \(\sigma: 2 \rightarrow 3\) Power: 81\% \(\rightarrow\) 47\%
- Significance level (\(\alpha\))
  - \(\alpha : 0.05 \rightarrow 0.01\) Power: 81\% \(\rightarrow\) 69\%
  - \(\alpha : 0.05 \rightarrow 0.10\) Power: 81\% \(\rightarrow\) 94\%
Power Changes

• $2n = 32$, 2 sample test, 81% power, $\delta = 2$, $\sigma = 2$, $\alpha = 0.05$, 2-sided test
• Difference to be detected ($\delta$)
  – $\delta : 2 \rightarrow 1$ Power: 81% → 29%
  – $\delta : 2 \rightarrow 3$ Power: 81% → 99%
• Sample size ($n$)
  – n: 32 → 64 Power: 81% → 98%
  – n: 32 → 28 Power: 81% → 75%
• Two-tailed vs. One-tailed tests
  – Power: 81% → 68%

Power should be….?

• Phase III: industry minimum = 80%
• Some say Type I error = Type II error
• Many large “definitive” studies have power around 99.9%
• Omics studies: aim for high power because Type II error a bear!

Power Formula

• Depends on study design
• Not hard, but can be VERY algebra intensive
• May want to use a computer program or statistician
Outline

✓ Power

➢ Basic Sample Size Information
  • Examples (see text for more)
  • Changes to the basic formula
  • Multiple comparisons
  • Rejected sample size statements
  • Conclusion and Resources

Basic Sample Size

• Changes in the difference of interest have HUGE impacts on sample size
  – 20 point difference → 25 patients/group
  – 10 point difference → 100 patients/group
  – 5 point difference → 400 patients/group

• Changes in difference to be detected, $\alpha$, $\beta$, $\sigma$, number of samples, if it is a 1- or 2-sided test can all have a large impact on your sample size calculation

Basic 2-Arm Study's

TOTAL Sample Size = \[
N = \frac{(Z_{\alpha/2} + Z_{\beta})^2 \sigma^2}{\delta^2}
\]

Basic Sample Size Information

• What to think about before talking to a statistician

• What information to take to a statistician
  – In addition to the background to the project
Nonrandomized?

• Non-randomized studies looking for differences or associations
  – Require larger sample to allow adjustment for confounding factors
• Absolute sample size is of interest
  – Surveys sometimes take % of population approach

Comments

• Study’s primary outcome
  – Basis for sample size calculation
  – Secondary outcome variables considered important? Make sure sample size is sufficient
• Increase the ‘real’ sample size to reflect loss to follow up, expected response rate, lack of compliance, etc.
  – Make the link between the calculation and increase
• Always round up
  – Sample size = 10.01; need 11 people

Sample Size in Clinical Trials

• Two groups
• Continuous outcome
• Mean difference
• Similar ideas hold for other outcomes
Sample Size Formula Information

- Variables of interest
  - type of data e.g. continuous, categorical
- Desired power
- Desired significance level
- Effect/difference of clinical importance
- Standard deviations of continuous outcome variables
- One or two-sided tests

Sample Size & Data Structure

- Paired data
- Repeated measures
- Groups of equal sizes
- Hierarchical or nested data
- Biomarkers
- Validity (of what) studies

Sample Size & Study Design

- Randomized controlled trial (RCT)
  - Block/stratified-block randomized trial
  - Cluster randomized (etc)
- Equivalence, non-inferiority, superiority trial
- Non-randomized intervention study
- Observational study
- Prevalence study
- Measuring sensitivity and specificity
Outline

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  - Examples (see text for more)
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  - Multiple comparisons
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  - Conclusion and Resources

How many humans do I need?
Short Helpful Hints

- Not about power, about stability of estimates
- 15/arm minimum: good rule of thumb for early studies
  - 12-15 gives somewhat stable variance, sometimes
  - If using Bayesian analysis techniques at least 70/arm
- If n < 20-30, check t-distribution
- Minimum 10 participants/variable
  - Maybe 100 per variable

Live Statistical Consult!

- Sample size/Power calculation: cholesterol in hypertensive men example (Hypothesis Testing lecture)
- Choose your study design
  - Data on 25 hypertensive men (mean 220, s=38.6)
  - 20-74 year old male population: mean serum cholesterol is 211 mg/ml with a standard deviation of 46 mg/ml
Example

- Calculate power with the numbers given
- What is the power to see a 9 point difference in mean cholesterol with 25 people in
  - Was it a single sample or 2 sample example?

Sample Size Rulers

JAVA Sample Size
Put in 1-Sample Example #s

- 1 arm, t-test
- Sigma (sd) = 38.6
- True difference of means = 220-211=9
- n=25
- 2 sided (tailed) alpha = 0.05
  - Power=XXXX
- 90% power
  - Solve for sample size n=XXXX

Move the Values Around

- Sigma (standard deviation, sd)
- Difference between the means

Different Study
Put in 2-Sample Example #s

- 2 arms, t-test
- Equal sigma (sd) in each arm = 2
- 2 sided (tailed) alpha = 0.05
- True difference of means = 1
- 90% power
- Solve for sample size

Keep Clicking “OK” Buttons

Phase I: Dose Escalation

- Dose limiting toxicity (DLT) must be defined
- Decide a few dose levels (e.g. 4)
- At least three patients will be treated on each dose level (cohort)
- Not a power or sample size calculation issue
Phase I (Old Way)

- Enroll 3 patients
- If 0 out of 3 patients develop DLT
  - Escalate to new dose
- If DLT is observed in 1 of 3 patients
  - Expand cohort to 6
  - Escalate if 0 out of the 3 new patients do not develop DLT (i.e. 1/6 at that dose develop DLT)

Phase I (cont.)

- Maximum Tolerated Dose (MTD)
  - Dose level immediately below the level at which ≥2 patients in a cohort of 3 to 6 patients experienced a DLT
- Usually go for “safe dose”
  - MTD or a maximum dosage that is pre-specified in the protocol
Phase I

Enroll 3 people

- 0/3 DLT: Escalate to new dose
- 1/3 DLT: Enroll 3 more at same dose
- 2 or 3/3 DLT: Stop

- 0/new 3 DLT: Escalate to new dose
- 1 or more/new 3 DLT: Drop down dose; start over
- Stop

0/3 DLT: Escalate to new dose
1/3 DLT: Enroll 3 more at same dose
2 or 3/3 DLT: Stop

0/new 3 DLT: Escalate to new dose
1 or more/new 3 DLT: Drop down dose; start over
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Phase I

Enroll 3 people

- 0/3 DLT
  - Escalate to new dose

- 1/3 DLT
  - Enroll 3 more at same dose
  - 0/new 3 DLT
    - Escalate to new dose
    - Stop
  - 1 or more / new 3 DLT
    - Stop

- 2 or 3 / 3 DLT
  - Drop down dose; start over

Stop

0/3 DLT

1/3 DLT

2 or 3 / 3 DLT

Stop

Drop down dose; start over

Enroll 3 more at same dose

0/new 3 DLT

1 or more / new 3 DLT

Stop
**Phase I Note**

- *Implicitly targets a dose with Pr (Toxicity) ≤ 0.17; if at 1/3+1/3 decide current level is MTD then the Pr (Toxicity) ≤ 0.33*
- Entry of patients to a new dose level does not occur until all patients in the previous level are beyond a certain time frame where you look for toxicity
- Not a power or sample size calculation issue

**Phase I**

- MANY new methods
- Several randomize to multiple arms
- Several have control arms
- Several have 6-15 people per arm

<table>
<thead>
<tr>
<th>Number of pts with DLT</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>0/3</td>
<td>Escalate one level</td>
</tr>
<tr>
<td>1/3</td>
<td>Enroll 3 more at current level</td>
</tr>
<tr>
<td>0/3 + 0/3 (To get here a de-escalation rule must have been applied at the next higher dose level)</td>
<td>STOP and choose current level as MTD</td>
</tr>
<tr>
<td>1/3 + 0/3</td>
<td>Escalate one level (unless a de-escalation rule was applied at next higher level, in which case choose current level as MTD)</td>
</tr>
<tr>
<td>1/3 + 1/3 or 2/3 or 3/3</td>
<td>STOP* and choose previous level as MTD (unless previous level has only 3 patients, in which case treat 3 more at previous level)</td>
</tr>
<tr>
<td>2/3 or 3/3</td>
<td>STOP and choose previous level as MTD (unless previous level has only 3 patients, in which case treat 3 more at previous level)</td>
</tr>
</tbody>
</table>
Phase II Designs

- Screening of new therapies
- Not to prove ‘final’ efficacy, usually
  - Efficacy based on surrogate outcome
- Sufficient activity to be tested in a randomized study
- Issues of safety still important
- Small number of patients (still may be in the hundreds total, but maybe less than 100/arm)

Phase II Design Problems

- Might be unblinded or single blinded treatment
- Placebo effect
- Investigator bias
- Regression to the mean

Phase II: Two-Stage Optimal Design

- Seek to rule out undesirably low response probability
  - E.g. only 20% respond (p0=0.20)
- Seek to rule out p0 in favor of p1; shows “useful” activity
  - E.g. 40% are stable (p1=0.40)
Phase II Example:
Two-Stage Optimal Design

- Single arm, two stage, using an optimal design & predefined response
- Rule out response probability of 20% (H0: p=0.20)
- Level that demonstrates useful activity is 40% (H1:p=0.40)
- $\alpha = 0.10$, $\beta = 0.10$

Two-Stage Optimal Design

- Let $\alpha = 0.1$ (10% probability of accepting a poor agent)
- Let $\beta = 0.1$ (10% probability of rejecting a good agent)
- Charts in Simon (1989) paper with different $p_1 - p_0$ amounts and varying $\alpha$ and $\beta$ values

Table from Simon (1989)
Phase II Example

- Initially enroll 17 patients.
  - 0-3 of the 17 have a clinical response then stop accrual and assume not an active agent
- If $\geq 4/17$ respond, then accrual will continue to 37 patients

Phase II Example

- If 4-10 of the 37 respond this is insufficient activity to continue
- If $\geq 11/37$ respond then the agent will be considered active
- Under this design if the null hypothesis were true (20% response probability) there is a 55% probability of early termination

**Blow up: Simon (1989) Table**

<table>
<thead>
<tr>
<th>$p_0$</th>
<th>$p_1$</th>
<th>$-\log_{10}(p_0)$</th>
<th>$-\log_{10}(p_1)$</th>
<th>$\text{EN}(p_0)$</th>
<th>$\text{PET}(p_0)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05</td>
<td>0.25</td>
<td>0.9</td>
<td>1.9</td>
<td>2.3</td>
<td>1.4</td>
</tr>
<tr>
<td>0.10</td>
<td>0.50</td>
<td>1.0</td>
<td>2.0</td>
<td>3.7</td>
<td>2.7</td>
</tr>
<tr>
<td>0.15</td>
<td>0.60</td>
<td>1.2</td>
<td>3.0</td>
<td>5.5</td>
<td>4.4</td>
</tr>
<tr>
<td>0.20</td>
<td>0.60</td>
<td>1.3</td>
<td>3.6</td>
<td>7.7</td>
<td>6.9</td>
</tr>
</tbody>
</table>
Sample Size Differences

- If the null hypothesis (H₀) is true
- Using two-stage optimal design
  - On average 26 subjects enrolled
- Using a 1-sample test of proportions
  - 34 patients
  - If feasible
- Using a 2-sample randomized test of proportions
  - 86 patients per group

Phase II

- Newer methods are available
- Many cite Simon (thus, why we went through it)

Phase II: Historical Controls

- Want to double disease X survival from 15.7 months to 31 months.
- \( \alpha = 0.05 \), one tailed, \( \beta = 0.20 \)
- Need 60 patients, about 30 in each of 2 arms; can accrue 1/month
- Need 36 months of follow-up
- Use historical controls
Phase II: Historical Controls

• Old data set from 35 patients treated at NCI with disease X, initially treated from 1980 to 1999
• Currently 3 of 35 patients alive
• Median survival time for historical patients is 15.7 months
• Almost like an observational study
• Use Dixon and Simon (1988) method for analysis

Phase II Summary

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 arm</td>
<td>Small n</td>
<td>No control</td>
</tr>
<tr>
<td>1 arm 2-stage</td>
<td>Small n, stop early</td>
<td>No control, correct responder/non responder rules</td>
</tr>
<tr>
<td>Historical controls</td>
<td>Small n, some control</td>
<td>Accurate control</td>
</tr>
<tr>
<td>2(+) arm</td>
<td>Control</td>
<td>Larger n</td>
</tr>
<tr>
<td>8 arm</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

Phase III Survival Example

• Primary objective: determine if patients with metastatic melanoma who undergo Procedure A have a different overall survival compared with patients receiving standard of care (SOC)
• Trial is a two arm randomized phase III single institution trial
Number of Patients to Enroll?

• 1:1 ratio between the two arms
• 80% power to detect a difference between 8 month median survival and 16 month median survival
• Two-tailed $\alpha = 0.05$
• 24 months of follow-up after the last patient has been enrolled
• 36 months of accrual
Phase III Survival

- Look at nomograms (Schoenfeld and Richter). Can use formulas
- Need 38/arm, so let’s try to recruit 42/arm – total of 84 patients
- Anticipate approximately 30 patients/year entering the trial

Non-Survival Simple Sample Size

- Start with 1-arm or 1-sample study
- Move to 2-arm study
- Study with 3+ arms cheat trick
  - Calculate PER ARM sample size for 2-arm study
  - Use that PER ARM
  - Does not always work; typically ok
1-Sample N Example

- Study effect of new sleep aid
- 1 sample test
- Baseline to sleep time after taking the medication for one week
- Two-sided test, $\alpha = 0.05$, power = 90%
- Difference = 1 (4 hours of sleep to 5)
- Standard deviation = 2 hr

Sleep Aid Example

- 1 sample test
- 2-sided test, $\alpha = 0.05$, 1-\(\beta\) = 90%
- $\sigma = 2$ hr (standard deviation)
- $\delta = 1$ hr (difference of interest)

Sample Size: Change Effect or Difference

- Change difference of interest from 1hr to 2 hr
- n goes from 43 to 11
Sample Size: Iteration and the Use of $t$
- Found $n = 11$ using $Z$
- Use $t_{10}$ instead of $Z$  
  - $t_{n-1}$ for a simple 1 sample
- Recalculate, find $n = 13$
- Use $t_{12}$
- Recalculate sample size, find $n = 13$  
  - Done
- Sometimes iterate several times

Sample Size: Change Power
- Change power from 90% to 80%
- $n$ goes from 11 to 8
- (Small sample: start thinking about using the $t$ distribution)

Sample Size: Change Standard Deviation
- Change the standard deviation from 2 to 3
- $n$ goes from 8 to 18
**Sleep Aid Example: 2 Arms**
**Investigational, Control**
- Original design (2-sided test, $\alpha = 0.05$, $1-\beta = 90\%$, $\sigma = 2\text{hr}$, $\delta = 1\text{hr}$)
- Two sample randomized parallel design
- Needed 43 in the one-sample design
- In 2-sample need twice that, in each group!
- 4 times as many people are needed in this design

**Aside: 5 Arm Study**
- Sample size per arm = 85
- $85 \times 5 = 425$ total
  - Similar 5 arm study
  - Without considering multiple comparisons
Sample Size: Change Effect or Difference
- Change difference of interest from 1hr to 2 hr
- n goes from 170 to 44

Sample Size: Change Power
- Change power from 90% to 80%
- n goes from 44 to 32

Sample Size: Change Standard Deviation
- Change the standard deviation from 2 to 3
- n goes from 32 to 72
Conclusion

• Changes in the difference of interest have HUGE impacts on sample size
  – 20 point difference → 25 patients/group
  – 10 point difference → 100 patients/group
  – 5 point difference → 400 patients/group
• Changes in difference to be detected, $\alpha$, $\beta$, $\sigma$, number of samples, if it is a 1- or 2-sided test can all have a large impact on your sample size calculation

2-Arm Study’s TOTAL Sample Size =

Other Designs?

Sample Size: Matched Pair Designs

• Similar to 1-sample formula
• Means (paired t-test)
  – Mean difference from paired data
  – Variance of differences
• Proportions
  – Based on discordant pairs
Examples in the Text

- Several with paired designs
- Two and one sample means
- Proportions
- How to take pilot data and design the next study

Cohen's Effect Sizes

- Large (.8), medium (.5), small (.2)
- Popular especially in social sciences
- Do NOT use unless no choice
  - Need to think
- 'Medium' yields same sample size regardless of what you are measuring

Outline

- Power
- Basic sample size information
- Examples (see text for more)
  - Changes to the basic formula/Observational studies
- Multiple comparisons
- Rejected sample size statements
- Conclusion and Resources
Unequal #s in Each Group

- Ratio of cases to controls
- Use if want $\lambda$ patients randomized to the treatment arm for every patient randomized to the placebo arm
- Take no more than 4-5 controls/case

$$n_2 = \lambda n_1 \rightarrow \lambda \text{ controls for every case}$$

$$n = \frac{(Z_{\alpha/2} + Z_{1-\beta})^2(\sigma_1^2 + \sigma_2^2 / \lambda)}{\delta^2}$$

K:1 Sample Size Shortcut

- Use equal variance sample size formula: TOTAL sample size increases by a factor of $$(k+1)^2/4k$$
- Ex: Total sample size for two equal groups = 26; want 2:1 ratio
  - $26(2+1)^2(4*2) = 26*9/8 = 29.25 \approx 30$
  - 20 in one group and 10 in the other

Unequal #s in Each Group: Fixed # of Cases

- Only so many new devices
- Sample size calculation says $n=13$ per arm needed
- Only have 11 devices!
- Want the same precision
- $n_0 = 11$ device recipients
- $kn_0 = \# \text{ of controls}$
How many controls?

\[ k = \frac{n}{2n_0 - n} \]

- \( k = \frac{13}{2 \times 11 - 13} = \frac{13}{9} = 1.44 \)
- \( kn_0 = 1.44 \times 11 \approx 16 \) controls (and 11 cases) = 27 total (controls + cases)
  - Same precision as 13 controls and 13 cases (26 total)

# of Events is Important

- Cohort of exposed and unexposed people
- Relative Risk = \( R \)
- Prevalence in the unexposed population = \( \pi_1 \)

Formulas and Example
# of Covariates and # of Subjects

- At least 10 subjects for every variable investigated
  - In logistic regression
  - No general theoretical justification
  - This is stability, not power
  - Peduzzi et al., (1985) unpredictable biased regression coefficients and variance estimates
- Principal component analysis (PCA) (Thorndike 1978 p 184): $N \geq 10m + 50$ or even $N \geq m^2 + 50$

Balanced Designs: Easier to Find Power / Sample Size

- Equal numbers in two groups is the easiest to handle
- If you have more than two groups, still, equal sample sizes easiest
- Complicated design = simulations
  - Done by the statistician

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Multiple Comparisons

- If you have 4 groups
  - All 2 way comparisons of means
  - 6 different tests
- Bonferroni: divide $\alpha$ by # of tests
  - $0.025/6 \approx 0.0042$
  - Common method; long literature
- High-throughput laboratory tests

DNA Microarrays/Proteomics

- Same formula (Simon et al. 2003)
  - $\alpha = 0.001$ and $\beta = 0.05$
  - Possibly stricter
- Many other methods

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✓ Examples (see text for more)
✓ Changes to the basic formula
✓ Multiple comparisons
  ➢ Rejected sample size statements
✓ Conclusion and Resources
No, not from your grant application.....

- Statistics Guide for Research Grant Applicants
- St. George’s Hospital Medical School
  Department of Public Health Sciences
- EXCELLENT resource

Me, too! No, Please Justify N

- "A previous study in this area recruited 150 subjects and found highly significant results (p=0.014), and therefore a similar sample size should be sufficient here."
  - Previous studies may have been 'lucky' to find significant results, due to random sampling variation

No Prior Information

- "Sample sizes are not provided because there is no prior information on which to base them."
  - Find previously published information
  - Conduct small pre-study
  - If a very preliminary pilot study, sample size calculations not usually necessary
Variance?

• No prior information on standard deviations
  – Give the size of difference that may be detected in terms of number of standard deviations

Number of Available Patients

• "The clinic sees around 50 patients a year, of whom 10% may refuse to take part in the study. Therefore over the 2 years of the study, the sample size will be 90 patients."
  – Although most studies need to balance feasibility with study power, the sample size should not be decided on the number of available patients alone.
  – If you know # of patients is an issue, can phrase in terms of power

Outline

✓ Power
✓ Basic Sample Size Information
✓ Examples (see text for more)
✓ Changes to the basic formula
✓ Multiple comparisons
✓ Rejected sample size statements
➢ Conclusion and Resources
Conclusions:
What Impacts Sample Size?

• Difference of interest
  – 20 point difference → 25 patients/group
  – 5 point difference → 400 patients/group

• \( \sigma, \alpha, \beta \)

• Number of arms or samples
• 1- or 2-sided test

Total Sample Size 2-Armed/Group/Sample Test

\[
N = \frac{4(z_{\alpha/2} + z_{\beta})^2 \sigma^2}{\delta^2}
\]

No Estimate of the Variance?

• Make a sample size or power table
• Make a graph
• Use a wide variety of possible standard deviations
• Protect with high sample size if possible

Top 10 Statistics Questions

10. Exact mechanism to randomize patients
8. Blinded/masked personnel
   ✓ Endpoint assessment
Top 10 Statistics Questions

7. Each hypothesis
   - Specific analyses
   - Specific sample size

6. How / if adjusting for multiple comparisons

5. Effect modification

Top 10 Statistics Questions

4. Interim analyses (if yes)
   - What, when, error spending model / stopping rules
   - Accounted for in the sample size?

3. Expected drop out (%)

2. How to handle drop outs and missing data in the analyses?

Top 10 Statistics Questions

1. Repeated measures / longitudinal data
   - Use a linear mixed model instead of repeated measures ANOVA
   - Many reasons to NOT use repeated measures ANOVA; few reasons to use
   - Similarly generalized estimating equations (GEE) if appropriate
Analysis Follows Design

Questions → Hypotheses →
Experimental Design → Samples →
Data → Analyses → Conclusions

• Take all of your design information to a statistician early and often
  – Guidance
  – Assumptions

Another Take? Paul Wakim

• www.youtube.com/watch?v=Zl8tGWNcKLI
• Lecture for IPPCR course in Brazil September 2014
• More focused on later phase studies
• Excellent examples

Questions?
Resources: General Books

- Rosenthal (2006) *Struck by Lightning: The curious world of probabilities*

Resources: General/Text Books

- Simon et al. (2003) *Design and Analysis of DNA Microarray Investigations*. Springer Verlag

Sample Size Specific Tables

- Categorical data: Lemeshow et al. (1996) *Adequacy of sample size in health studies*. Wiley
Resources: Articles


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Regulatory Guidances

• ICH E9 Statistical principles
• ICH E10: Choice of control group and related issues
• ICH E4: Dose response
• ICH E8: General considerations
• US FDA guidance and draft guidance on drug interaction study designs (and analyses), Bayesian methods, etc.
  – http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234622.htm
Resources: URLs

- Sample size calculations simplified
  - http://www.jerrydallal.com/LHSP/SIZE.HTM
- Stat guide: research grant applicants, St. George’s Hospital Medical School
  (http://www-users.york.ac.uk/~mb55/guide/guide.htm)
  - http://tinyurl.com/7qpzp2j
- Software: nQuery, EpiTable, SeqTrial, PS
  (http://biostat.mc.vanderbilt.edu/wiki/bin/view/Main/PowerSampleSize)
  - http://tinyurl.com/zoysm
- Earlier lectures

Various Sites by Steve Simon

- www.pmean.com/category/HumanSideStatistics.html
- www.pmean.com/category/RandomizationInResearch.html
- www.pmean.com/category/SampleSizeJustification.html
- http://www.cs.uiowa.edu/~rlenth/Power/